REMARKS/ARGUMENTS

35 U.S.C. § 112, first paragraph

Claims 1-8, 12-13, and 16-17 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a bioactive agent comprising CCFA, is allegedly not enabling for one to three bioactive agents. Applicants respectfully disagree. However, in order to advance prosecution, Applicants hereby amend the claims to a composition comprising crystalline ceftiofur free acid.

35 U.S.C. § 103(a) Dunn (US 5,721,359) in view of Foster (US 5,736,151)

Claims 1-8, 12-13, and 16-17 are rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Dunn (US 5,721,359) in view of Foster (US 5,736,151). In referring to Dunn, the Examiner further states that "Dunn teaches modifying the oil carrier by heat or irradiation in order to render it sterile, see column 8, lines 42-50." Applicants respectfully disagree. The passage in question reads (column 8 lines 42 to 50):

> "Carriers and vehicles include vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols, for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like. Any solid preparations for subsequent extemporaneous preparation of sterile injectable preparations are sterilized, by exposure to heat, cobalt 60 irradiation, or by exposure to a sterilizing gas, for example, ethylene oxide."

The issue is whether the phrase "solid preparations" refers to solids in a carrier or simply solids. If the term "solid preparations" refers simply to solids, then the carrier is not present when these preparations are being irradiated or heated. Dunn discloses three methods for sterilizing the solid preparations, that is, heat, cobalt 60 irradiation, and exposure to ethylene oxide. As noted in Remington, The Science and Practice of Pharmacy (19th Edition p. 765), ethylene oxide is not generally used to sterilize liquids. Ethylene oxide is toxic, carcinogenic, teratogenic, and difficult to remove from the objects being sterilized, and ethylene oxide residues are not desirable in a pharmaceutical product. Products sterilized with ethylene oxide need to be quarantined for about fourteen days to eliminate the absorbed residues of ethylene oxide. As

noted in the Matheson Tri-Gas MSDS for ethylene oxide, it is soluble in water and organic solvents. Thus, if ethylene oxide were used to sterilize a solid in one of the carriers described by Dunn, it would dissolve in the carrier and would not be readily removed. However, ethylene oxide may be used to sterilize solid preparations. Accordingly, the fact that ethylene oxide sterilization is listed as a possible method of sterilization for the solid preparations indicates that these solid preparations are solids and not solids in a carrier.

Applicants also note that in the passage above, Dunn refers to "solid preparations for subsequent extemporaneous preparation of sterile injectable preparations..." Clearly, the term "solid preparations" does not refer to solids in a carrier because these preparations require further steps to produce "sterile injectable preparations." If a carrier were present, the preparations would be suitable for injection, and would not require further processing.

Applicants further respectfully submit that the term "solid preparations" refers to a dosage form. Dosage forms are discussed in Dunn (column 8 lines 14 to 20):

> Examples of suitable dosage unit forms in accordance with this invention are liquid preparations in suitable liquid vehicles for intramuscular, intramammary and intravenous administration, suppositories and sterile dry preparations for the extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations in a suitable liquid vehicle or for administration as a solid implant.

Applicants respectfully submit that the person skilled in the art would conclude that in the passage in Dunn, quoted above, the term "solid preparations for subsequent extemporaneous preparation of sterile injectable preparations" (column 8 lines 47 to 48) refers to the dosage form described as "sterile dry preparations for subsequent extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations" (Column 8 lines 17 to 19). Clearly this dosage form is a dry solid, and Applicants respectfully submit that the "solid preparations" (column 8 line 47) are dry solids. Since the carrier is not present when the solid preparations are being sterilized, the carrier is not subject to heat or irradiation. Thus, Dunn does not teach the modified vehicles used in Applicants' invention.

Applicants respectfully disagree with the Examiner's assertion that "Dunn teaches modifying the oil carrier by heat or irradiation..." Applicants further disagree with the examiner's conclusion that because Dunn discloses heat that the peroxide level is inherent. First,

as pointed out above the material being heated is a solid and not a carrier. Second, even if it is deemed that a carrier is present Applicants respectfully submit that heating does not inherently produce the claim peroxide levels. To show inherency, the extrinsic evidence must make it clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that the person skilled in the art would recognize that fact (*In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999)). Inherency cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency (*In re Robertson*, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999)). Occasional results are not inherent (*Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1365, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999)). Even a prior art reference showing the same layered structure as the invention under consideration is not sufficient to show that the prior art reference inherently discloses the invention (*Crown Oper. Int'l Inc. v. Solutia Inc.*, 62 USPQ2d 1917 (Fed. Cir. 2002)).

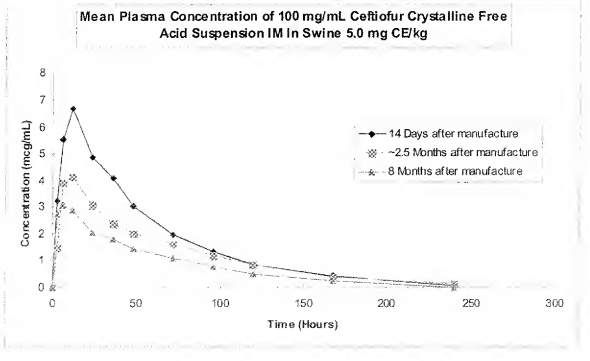
Even if a carrier were heated in Dunn, the Examiner has provided no explanation of why heating a carrier inherently produces a peroxide value of between about 10 to about 600 millicquivalents (mEq) of peroxide per 1000 grams of oil. The Examiner has provided no explanation of why that level of peroxide is necessarily produced during heat sterilization and the person skilled in the art would recognize that fact as required by *In re Robertson*, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999). The Examiner has provided no example in which heat sterilization produces the peroxide levels set forth in the claims, and more particularly that production of the required level of peroxides is more than an occasional result as required by *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1365, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999). Applicants respectfully suggest that the Examiner's assertion of inherency without any further discussion or showing of facts does not meet the standards set by the courts for an inherency rejection.

Foster teaches a formulation containing ceftiofur HCl in an oil carrier that includes a small amount of water (column 5 lines 8 to 18). Foster does not teach a formulation comprising a modified carrier. Foster also recommends dosing once a day (column 8 lines 16 to 18), and thus provides an immediate release formulation, not a sustained release formulation. Neither

Dunn nor Foster provide for a modified carrier. Taken separately or together, the two references do not provide a teaching of Applicants' invention.

Applicants respectfully note that the compositions of Dunn (US 5,721,359) does not provide sustained release performance of the compositions of the present invention. Specifically, the compositions of Dunn do not provide predictable sustained release of one or more bioactive agents upon administration immediately after manufacture of the composition and throughout their shelf life. A formulation containing 100 mg/ml crystalline ceftiofur free acid was prepared according to example 4 of Dunn. The formulation was administered intramuscularly to swine at 14 days, approximately 2.5 months and 8 months after preparation at a dose of 5.0 mg of ceftiofur equivalent (CE)/kg body weight. Although there were no noticeable changes in the formulation's potency, the release profile of the formulation changed noticeably over time. This is illustrated by the following graph.

In-vivo Drug Release Profile Changes Over Time for 100 mg/ml Crystalline Ceftiofur Free Acid Formulation of the Dunn Patent Administered IM in Swine



Since the formulation of Dunn does not produce the same results as the formulations of the present invention, the combination of Dunn and Foster will not produce Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Applicants respectfully request reconsideration and withdrawal of all rejections. Allowance of the present application is earnestly requested.

The Commissioner is hereby authorized to debit Deposit Account No. 16-1445 for any underpayments overseen by Applicants in relation to this response.

If the Examiner believes that personal communications will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this application is respectfully requested.

Respectfully submitted,

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